A Seismic Shift in Staging

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Appropriately staging lung cancer is critical for at least four reasons. First, the staging system provides a standardized description of the disease, a common language, if you will, for different physicians in different health care settings to understand the extent of a given patient’s disease. Second, and perhaps the most important rationale for staging, is that stage dictates treatment and the treatment regimens vary considerably by stage. For example, currently stage 1A lung cancer is treated with surgery alone, stage 2 and resected stage 3A lung cancers are treated surgically followed by adjuvant chemotherapy, bulky stage 3A lung cancer is treated with combination chemoradiotherapy, and metastatic lung cancer is treated with chemotherapy alone. Third, in a crude way, stage predicts survival. Fourth, the staging system allows us to facilitate research and compare results of different clinical trials. Historically, much credit should be given to the pioneers who described and revised the current staging system in lung cancer. It is through their efforts that we were able to provide a framework for treating those with lung cancer and a base on which to build cancer clinical trials. In 1974, the first TNM staging classification for non-small cell lung cancer was undertaken by the American Joint Committee for Cancer Staging (AJCC). It was based on analysis of 2155 patients with lung cancer. In 1986, members of the AJCC, the Union Internationale Contre le Cancer (UICC), as well as Japanese and German representatives proposed a revised international staging system for lung cancer based on analysis of 3753 lung cancer patients who had care provided at the M.D. Anderson Cancer Center and the North American Lung Cancer study group’s reference center for anatomic and pathologic classification of lung cancer. The most recent revision, published in 1997, was based on 5319 patients treated for lung cancer between 1975 and 1988 at the aforementioned sites. Several important changes were made to the most recent staging system. Stages I and II were divided into IA and IB and IIA and IIB, respectively. T3N0M0 was down-staged to stage IIB. Tumors with satellite nodules in the same lobe were designated as T4 (and thus stage 3B), and those with a primary tumor and satellite nodules in other lobes were designated M1. The current staging system has been in place for 10 years, having undergone two major revisions since its introduction in 1974.

Although this classification system has served us well, there are clearly limitations. Many of the data on which the staging system is based are single-institution data, from a dedicated cancer center, with expertise in accurately staging patients with lung cancer. Unfortunately, the data set represents a small geographic area in North America and one wonders whether the results are generalizable to other parts of the world. Further, many of the cases were surgical cases. Although 5000 or so cases of lung cancer may seem like enough, there were instances in which certain clinical presentations (e.g., primary tumors with satellite nodules) had very few cases available for analysis. Last, although the data were internally validated, extensive external validation using other data sets was not performed.

This leads us to to the to the massive undertaking of the International Association for the Study of Lung Cancer and the article by Goldstraw et al. in this issue of the Journal of Thoracic Oncology. They propose for consideration a revision of the TNM stage groupings that addresses some of the methodologic pitfalls of the current system and a few
of the clinical scenarios that needed clarification and perhaps new classification.\textsuperscript{7–9} The methodology deserves a closer look. An international staging committee was formed with worldwide expert multidisciplinary representation in thoracic oncology forming the nucleus. Equally critical to the success of this project was that they were supported by the Cancer Research and Biostatistics group with extensive expertise in managing and analyzing cancer data sets. There are more than 100,000 entries in the data set representing 23 institutions in 12 countries in Europe, North America, and Australasia. To say that the data are robust would be an understatement. In my view, the most important component of their work was the painstaking validation of their findings. That is to say that when changes in the staging system were proposed based on survival, they were both internally validated using a subset of the larger data set and externally validated using the Surveillance Epidemiology and End Results cancer registry. Are the data perfect? Not really. Many of the data entered were not collected with the expressed purpose of staging lung cancer, and some of the data are incomplete. In the future, a prospective database will overcome this obstacle. Is this the best data set available? Absolutely, and it is generalizable to patients with lung cancer all over the world.

Some of the changes that they propose make eminent clinical sense. The main suggestions are in the T and M classification with N status remaining the same. They found that tumor size was an important prognosticator and recommend that the T factor be subdivided based on five different-size criteria. Because survivorship was better, they recommend reclassification of primary tumors with satellite nodules in the same lobe from T4 to T3 and that additional nodules in one lobe of the ipsilateral lung moved from a M1 in the same lobe from T4 to T3 and that additional nodules in the same lobe from T4 to T3 and that additional nodules in one lobe of the ipsilateral lung moved from an M1 designation to T4. Malignant pleural effusion is currently classified as T4 or so-called wet 3B disease, despite the fact that the survival of patients in this group is much more like that of metastatic rather than locally advanced disease. They appropriately propose moving these patients to M1. One final change is that they recommend the M status be split into M1a (metastatic disease confined to the chest) and M1b (extrathoracic metastatic disease) based on the finding that survival is better in those with metastatic disease confined to the thorax.

If these recommendations are adopted, how long are they likely to last? That is hard to say. Even with the size and scope of this undertaking, the staging system remains a relatively crude predictor of survival. Recent forays into tumor protein expression and cancer genomics have provided a glimpse into how we may improve our ability to predict outcome among those within a given stage grouping.\textsuperscript{10–12} One can envision a time in the not too distant future when stage will be based on both the TNM classification and molecular diagnostics. Until then, let us admire the work of those who built the staging system over the past 30 years and embrace the proposal for a new classification for lung cancer.

REFERENCES